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IARC Carcinogen Update

We recently published an article in which we presented a list of occupational carcinogens (Siemiatycki et al. 2004), based on the International Agency for Research on Cancer (IARC) Monographs Program. Our review covered Volumes 1–83 of the *IARC Monographs*. However, because the IARC Monograph Program is ongoing, the list of occupational carcinogens will need to be periodically updated. Since we completed our article, there have been three Monograph meetings that addressed substances that can be classified as occupational; therefore, we would like to notify readers of some important changes in the list of occupational carcinogens. Table 1 shows summary information about occupational substances and mixtures that were recently evaluated by IARC as human carcinogens (group 1), probable human carcinogens (group 2A), or possible human carcinogens (group 2B). As we did in our earlier article (Siemiatycki et al. 2004), we added to the IARC evaluations our assessment of the main occupations in which the agent may be found and the target organ for carcinogenicity.

Volume 86 focuses on cobalt in hard-metals and cobalt sulfate, gallium arsenide, indium phosphide, and vanadium pentoxide (IARC, in press a). In our article (Siemiatycki et al. 2004), cobalt and cobalt compounds were listed as Group 2B human carcinogens.

In IARC's recent evaluation (IARC, in press a), cobalt metal with tungsten carbide is classified in Group 2A, whereas cobalt metal without tungsten carbide, cobalt sulfate, and other soluble cobalt(II) salts remain in Group 2B. Three substances for which there were no previous IARC evaluations have now been evaluated and classified: gallium arsenide is classified as a Group 1 human carcinogen, indium phosphide as a Group 2A (probable) human carcinogen, and vanadium pentoxide as a Group 2B (possible) human carcinogen (IARC, in press a).

Volume 87 (IARC, in press b) updates the prior evaluations on inorganic and organic lead compounds, which were included in Volume 23 (IARC 1980) and in Supplement 7 (IARC 1987). Previously, lead and inorganic lead compounds were classified in Group 2B, whereas organic lead compounds were classified in Group 3. The most recent IARC evaluation results in an upgrading of inorganic lead compounds to Group 2A; organic lead compounds remain in Group 3 (IARC, in press b). The Working Group, however, noted that part of the organic lead is metabolized into ionic lead, which would be expected to present the same toxicity as inorganic lead.

In Volume 88, formaldehyde was upgraded from a Group 2A (probable) to a Group 1 human carcinogen (IARC, in

press c; Coglian et al. 2005). The other two substances covered by this monograph, 2-butoxyethanol and 1-*tert*-butoxy-2-propanol, are evaluated as Group 3 (not classifiable).

The authors declare they have no competing financial interests.

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- IARC. In press b. Inorganic and Organic Lead Compounds. *IARC Monogr Eval Carcinog Risks Hum* 87.

Table 1. Substances and mixtures that have been evaluated by IARC as human carcinogens and that are occupational exposures, based on *Monograph* Volumes 84–90.

Substance or mixture	Occupation or industry in which the substance is found ^a	Site(s)	IARC classification	IARC Monograph
Cobalt metal with tungsten carbide	Production of cemented carbides (hard-metal industry); tool grinders; saw filers; diamond polishers	Lung ^b	2A	86
Cobalt metal without tungsten carbide	Miners; production of alloys; processing of copper and nickel ore; glass and ceramic production; welders of cobalt-containing alloys	Uncertain	2B	86
Cobalt sulfate and other soluble cobalt(II) salts	Electroplating and ceramic industries	Uncertain	2B	86
Gallium arsenide	Production; microelectronics industry (integrated circuits and optoelectronic devices)	Uncertain	1 ^c	86
Indium phosphide	Production; microelectronics industry (integrated circuits and optoelectronic devices)	Uncertain	2A ^d	86
Vanadium pentoxide	Ore refining and processing; chemical manufacturing industry; maintenance of oil-fired boilers and furnaces	Uncertain	2B	86
Inorganic lead compounds	Lead smelters; plumbers; solderers; occupations in battery recycling smelters; production of lead-acid batteries; printing press occupations; pigment production; construction and demolition	Lung ^b Stomach ^b	2A	87
Formaldehyde	Production; pathologists; medical laboratory technicians; plastics; textile and plywood industry	Nasopharynx ^e Leukemia ^b Nasal sinuses ^b	1	88

^aNot necessarily an exhaustive list of occupations/industries in which this agent is found; not all workers in these occupations/industries are exposed. The term "production" is used to indicate that this substance is man-made and that workers may be exposed in the production process. ^bWe judged that the evidence for an association with this site was suggestive. ^cIn reaching an overall evaluation of Group 1, the working group noted the potential for gallium arsenide to cause cancer through releases of a small amount of its arsenic, which behaves as inorganic arsenic at the sites where it is distributed. Arsenic and arsenic compounds have been evaluated as IARC Group 1, carcinogenic to humans. For arsenic in drinking water, the most recent IARC evaluation of arsenic [Volume 84; (IARC 2004)], there was sufficient evidence in humans that arsenic causes cancers of the urinary bladder, lung, and skin; the evidence for cancers of the liver and kidney was limited. ^dAbsence of data on cancer in humans; the final evaluation for carcinogenicity was upgraded from 2B to 2A based on evidence of carcinogenicity in experimental animals. ^eThe evidence was sufficient.

IARC. In press c. Formaldehyde, 2-Butoxyethanol and 1-tert-Butoxy-2-propanol. IARC Monogr Eval Carcinog Risks Hum 88.

Siemiatycki J, Richardson L, Straif K, Latreille B, Lakhani R, Campbell S, et al. 2004. Listing occupational carcinogens. *Environ Health Perspect* 112:1447–1459.

Indoor- and Outdoor-Generated Particles and Children with Asthma

In their article “Pulmonary Effects of Indoor- and Outdoor-Generated Particles in Children with Asthma,” Koenig et al. (2005) made use of their really interesting model that enables them to discern exposure from indoor- and outdoor-generated particles. They concluded that

The ambient-generated component of PM_{2.5} [particulate matter $\leq 2.5 \mu\text{m}$ in aerodynamic diameter] exposure is consistently associated with increases in eNO [exhaled nitric oxide] and the indoor-generated component is less strongly associated with eNO.

This finding should not lead to the assumption that particles generated indoors are in general not able to induce endogenous NO production. The authors themselves pointed out one limitation of their study:

Children in the Seattle panel study spent an average of 66% of their time indoors at home and 21% indoors away from home (primarily at school) ... (Koenig et al. 2005)

However, contribution of indoor sources to PM exposure was only estimated on the basis of measurement data from the subjects' residences. This could have led to uncertainties in the exposure assessment, biasing the effect estimates toward null.

I also want to mention the great variability in possible indoor sources of PM. In their article, Koenig et al. (2005) provided no information on the smoking status of household members. If the 19 children under study lived in nonsmoking households, the results might be true for this setting but not for others.

Finally, I suggest that time of measurement and exposure should be considered. If the children attend school in the morning, they might go home (maybe in high traffic) at noon or early afternoon for lunch.

[NO] samples were collected in the afternoon or early evening at the child's residence. Children were asked to forgo food intake for 1 hr before collection of exhaled breath.

If NO production peaks several hours after exposure, it could be possible that the children's exposure on their way home from school was the most influential one (not because of the origin of the particles but because of the study's lag structure). It would be interesting and rather rewarding to

study the short-term lag structure between PM exposure and both exhaled NO and lung function [for which Koenig et al. (2005) found an association with exposure due to sources in the residents' homes]. I would expect an increase of exhaled NO to be a rather late reaction to inflammatory stimuli. For example Rolla et al. (2004) reported that after aspirin inhalation by subjects with aspirin-inducible asthma, NO increased significantly reaching the peak value 4 hr after bronchoconstriction.

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Indoor- and Outdoor-Generated Particles: Koenig et al. Respond

We appreciate Moshhammer's comments and his interest in our research. We have several points to raise in reply.

In our article (Koenig et al. 2005), we stated that indoor sources are known to affect airway inflammation. We recognized that indoor sources vary greatly and that 19 homes may not provide a sufficient sample size to allow for a robust association. It is true that the children in our study spent substantial time away from home. We now have additional data from a panel of 16 adults (average age of 75 years) who did not commute or leave home regularly; in these adults we found the same coefficient with eNO (exhaled nitric oxide) versus outdoor PM_{2.5} (particulate matter $\leq 2.5 \mu\text{m}$ in aerodynamic diameter) as in the research in question (Jansen et al. 2004). In addition, Ebelt et al. (2005) found lung function decrements only with ambient particles in a group of non-smoking 54- to 86-year-old adults. These results provide additional evidence of an ambient-only pulmonary effect among individuals who spent relatively little time away from home.

Regarding smoking status, one inclusionary criterion for our study was to be a non-smoker and live with nonsmokers; thus smoking is not an important indoor source

of particles in these residences. Children in the Seattle school district do not go home for lunch. However, it is true that our exhaled breath samples were taken 1–2 hr after the commute home (Liu et al. 2003). On average, the time between morning commute and eNO collection was 9 hr; between afternoon commute and breath collection was about 2 hr. We are now looking at the short-term lag structure. Using a polynomial distributed lag model, we found that PM_{2.5} was associated with the eNO for up to 10–12 hr before the eNO measurement (Mar et al., in press).

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Blood Lead and IQ in Older Children

In their article about blood lead and IQ in older children, Chen et al. (2005) made the very important observation that IQ (intelligence quotient) in older children correlates better with their current blood lead level than with levels determined at 2 years of age. This observation has enormous public health implications in terms of defining who is at risk of cognitive decrement upon exposure to lead, and challenges the widely held assumption that the effects of lead on neuro-behavioral function are exclusively developmental. My colleagues and I (Carpenter et al. 2002) previously studied the effects of gestational and lactational exposure of rats to lead with measurement of long-term potentiation in hippocampal brain slices. Long-term potentiation is an electrophysiological measure of synaptic plasticity

that is widely viewed as being at least one component of learning and memory, and it is reduced upon *in vivo* lead exposure. To our surprise we also found that acute perfusion of low concentrations of lead onto brain slices from control animals resulted in reduction of long-term potentiation, suggesting that the effect is more pharmacologic than developmental. The results of Chen et al. (2005) in humans and our studies in rats suggest that lead causes both developmental and pharmacologic impairment of cognitive function. If this is true, then steps should be taken to prevent exposure to lead and to reduce lead levels in individuals of any age, not just young children.

The author declares he has no competing financial interests.

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Editor's note: In accordance with journal policy, Chen et al. were asked whether they wanted to respond to this letter, but they chose not to do so.

Comparison of Study Controls

In the article "Natural Variability and the Influence of Concurrent Control Values on the Detection and Interpretation of Low-Dose or Weak Endocrine Toxicities," Ashby et al. (2004) discounted a number of studies reporting low-dose effects caused by endocrine-disrupting chemicals, including bisphenol A (BPA), based on variability in

control values in experiments conducted at different times. They cited data from four experiments that we reported in three published studies (Ohsako et al. 2001; Sakaue et al. 1999, 2001). Ashby et al. stated that the marked reduction in daily sperm production (DSP) caused by BPA that we observed in two experiments (Sakaue et al. 2001) should be discounted because the DSP values in BPA-exposed males were not significantly different from those in controls we reported in another study (Ohsako et al. 2001). Ashby et al. (2004) proposed that our conclusion that BPA significantly decreased DSP is incorrect because of a difference in control values for DSP from different experiments conducted at different times.

We would like to point out that it is absolutely inappropriate to compare these sets of data not only because the experiments were conducted at different times but also because they included different experimental conditions and different animals (Table 1). First, we used Sprague-Dawley rats in the two experiments in the BPA study (Sakaue et al. 2001) and Holtzman rats in another study of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (Ohsako et al. 2001). Second, the Sprague-Dawley rats used in the BPA study were purchased from a laboratory animal breeder, whereas the Holtzman rats used in the TCDD experiment were bred at the National Institute for Environmental Studies (NIES). Third, animal maintenance conditions were not the same for the three studies: Holtzman rats were housed in polycarbonate cages with wooden chips, and Sprague-Dawley rats were kept in hanging stainless wire-mesh cages.

There are many reasons why males from different rat strains obtained from different breeding facilities using different animal feed and housing conditions might differ in DSP. We thus disagree with the interpretation by Ashby et al. (2004) that this variability between rats from different strains invalidates the conclusion drawn by Sakaue et al. (2001) that exposure to BPA reduces DSP in Sprague-Dawley rats. We also disagree with

their attempt to discount effects caused by BPA and other endocrine-disrupting chemicals due to variability in control animals from entirely different experiments in which low-dose effects were reported by other researchers.

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Study Controls: Ashby Responds

Figure 1 is the relevant summary figure (Figure 8) from our article (Ashby et al. 2004). Our point in the article, as well as now, is that it is incumbent upon each investigator to accept, to study, and where possible, to understand the extent, nature, and origins of variability (within and

Table 1. Comparison of conditions of the three experiments.

	Sakaue et al. 1999	Ohsako et al. 2001	Sakaue et al. 2001
Rat strains	Holtzman	Holtzman	Sprague Dawley
Place of birth	Animal breeding facility (NIES)	Chemical hazard area (NIES)	CLEA Japan
Age at the time of purchase	NA	NA	PND77
Cage type	Stainless wire-mesh	Polycarbonate plastic	Stainless wire-mesh
Bedding	None	Wood chip	None
Age at the time of tissue collection	PND126	PND120	PND126
Place for examination	Animal breeding facility (NIES)	Chemical hazard area (NIES)	Animal breeding facility (NIES)
Test compound	BPA	TCDD	BPA
Vehicle	Corn oil	Corn oil/4% <i>n</i> -nonane	Corn oil/6.5% ethanol
Control DSP value ^a (× 10 ⁶ /testis)	39.0 ± 1.6 (4)	34.6 ± 2.0 (12)	44.0 ± 2.2 (5) ^b 49.3 ± 5.3 (8) ^c

Abbreviations: NA, not applicable; PND, postnatal day.

^aMean ± SE (number of animals). ^bFirst experiment. ^cSecond experiment.

between experiments) of the critical assay parameter. If you do not know why the assay parameter varies naturally with time, or between experiments, it becomes difficult to interpret small perturbations of the parameter induced in a chemical toxicity study. This was the problem we faced when we tried to explain our inability, over four extensive studies (Ashby et al. 2003), to confirm the effects that Sakaue et al. (2001) reported for bisphenol A (BPA). The control values for daily sperm production (DSP) in Sprague-Dawley rats over our four experiments (Figure 1) varied little, despite the use of three different rodent diets and a variety of physical test conditions (changes in bedding and caging). We also noted (Ashby et al. 2004) that Sakaue et al. reported similar control DSP values for Holtzman rats (Sakaue et al. 1999) and Sprague-Dawley rats (Sakaue et al. 2001; Figure 1). The most interesting aspect of the data in Figure 1 is the extent of variability in control DSP values reported by Sakaue et al. (2001) for their two experiments on BPA in Sprague-Dawley rats. It is important to understand the origins of these variations in control DSP values between similar experiments before interpreting small chemically induced perturbations in DSP values with confidence. Equally, by paying attention to the

origins of control variability, we were able to show that two chemicals we had previously considered to be negative in the rodent uterotrophic assay were, in fact, weakly positive (Ashby et al. 2004). Stable control values for an assay lead to the generation of sound assay data.

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ERRATUM

In "Decrease in Anogenital Distance among Male Infants with Prenatal Phthalate Exposure" [Environ Health Perspect 113:1056–1061 (2005)], Shanna Swan's affiliation was listed as University of Rochester, Rochester, Minnesota. The correct location is Rochester, New York.

EHP regrets the error.

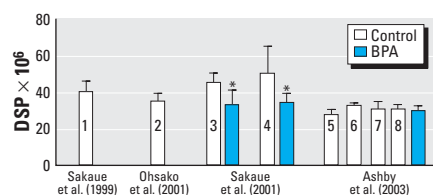




Figure 1. Comparison of control DSP (mean ± SD) reported from the same laboratory [Ohsako et al. (2001) and Sakaue et al. (1999, 2001)] and a different laboratory (Ashby et al. 2003) with the greatest effect induced by BPA (Sakaue et al. 2001). A range of BPA doses was used in these experiments, and only the dose that induced the greatest effect in each experiment is shown: 20 μ g/kg (Sakaue et al. 1999); 200 μ g/kg (Sakaue et al. 2001); 200 mg/kg (Ashby et al. 2003). The effect of BPA is not significantly different from the control reported by Ohsako et al. (2001; bar 2: one- or two-sided Student's *t*-test). Sakaue et al. (1999) and Ohsako et al. (2001) used Holtzman rats, and Sakaue et al. (2001) and Ashby et al. (2003) used Sprague-Dawley rats. However, the identical control DSP values for Holtzman rats (Sakaue et al. 1999, bar 1) and Sprague-Dawley rats (Sakaue et al. 2001; bar 3) indicate that rat strain is not a key variable on control DSP values and that, consequently, it is possible to compare data across strains and experiments for that laboratory. Reprinted from Ashby et al. (2004) with permission from *Environmental Health Perspectives*.

*Reported by Sakaue et al. (2001) as statistically different from the concurrent control (bars 3 and 4).



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